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# International Conference on Environmental Arsenic: An Overview

## by Bruce A. Fowler*

The National Institute of Environmental Health Sciences and the Department of Environmental Hygiene, Karolinska Institute, as Cooperating World Health Organization Centers in collaboration with the Scientific Commitee on the Toxicology of Metals under the Permanent Commission and International Association on Occupational Health, sponsored an International Conference on Arsenic October 5–8, 1976, in Fort Lauderdale, Florida, USA. The purpose of the conference was to assess the current level of scientific knowledge about arsenic as an environmental toxicant and to identify needed areas of research. This overview was assembled with the assistance of persons attending the conference, but final responsibility for the summary content and attached recommendations should be regarded as that of only the conference chairman.

The meeting was divided into consecutive sessions dealing with methods and problems of analysis, sources of environmental pollution, occurrence and transformation in nature, effects and dose-response relationships in humans, kinetics and metabolism, effects and dose-response relationships in animals. Each of these sessions is summarized below followed by recommendations for areas of future research.

## Methods and Problems of Analysis

### Summary

Reports presented during the analysis session indicated that various analytical techniques with low detection limits are presently available for the speciation of some arsenicals in air and water. These techniques have also been recently applied to some other matrices, and such studies should appear in the analytical literature in the near future. Analyses of arsenic in air seemed to indicate that current sampling and analytical techniques are adequate for inorganic arsenic oxides but not volatile organoarsenicals. Differential generation of arsines, gas chromatography, and combined gas chromatography–flameless atomic absorption were all used as methods capable of speciating arsenic with reasonable accuracy and precision. The application of these methods to biological matrices, however, requires further work into the effects of sample preparation on analysis.

### Recommendations

Present analytical speciation techniques should be applied to biological and other matrices requiring digestion or other preparative procedures. New analytical techniques capable of speciating other organoarsenicals in various matrices should be developed. Precision of arsenic analyses should be checked by interlaboratory calibration in a variety of matrices using a number of methods. Analytical laboratories with speciation capabilities should be asked to register themselves with information services of the World Health Organization (WHO) and EPA to aid those seeking such analyses.

## Sources of Environmental Pollution

### Summary

Important sources for emission of arsenic into the environment include nonferrous smelting operations and certain coal-fired power plants using arsenic rich coal. Such operations have been found to give rise to elevated concentrations of arsenic in air,

*National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709.

water, and soil in the vicinity of the source. During the plenary discussion session it was suggested that steel smelters, domestic burning of arsenic impregnated wood, and abandoned mines also be studied as anthropogenic sources of emission. Natural sources of environmental arsenic release such as volcanoes and hotsprings were also recognized as important.

### Recommendations

Further studies detailing the quantities and ultimate fate of arsenic from all these sources should be conducted.

## Occurrence and Transformation in Nature

### Summary

From papers presented in this session, it was obvious that an understanding of the methylation–demethylation cycle of arsenic in the environment was essential to predicting possible hazards from this element. On an overall mass basis, inorganic arsenate ($As^{+5}$) is the predominant form found in marine waters. Arsenic in marine organisms is present as lipid and water soluble organoarsenic compounds whose exact chemical structure and composition are presently unknown. Lipid-soluble forms can be converted to the water-soluble forms by treatment with acid. The main water-soluble form is highly stable and resistant to metabolic and chemical breakdown. In the terrestrial environment, extensive application of arsenical pesticides during the first-half of this century has caused a build-up of arsenic in some soils and the occasional contamination of some crops. The uptake of arsenic by plants appears to be related to the amount of soluble arsenic in soil, nature of the soil, and species of plant involved.

### Recommendations

Studies dealing with the rates and mechanisms of arsenic methylation-demethylation in both marine and terrestrial ecosystems are needed, as well as more information on general As cycling and flows in the environment.

## Effects and Dose-Response Relationships in Humans

### Summary

During this session, a number of acute, subacute, or chronic incidents of mass human arsenic poisoning were discussed. These events usually occurred as a result of arsenic exposure via contaminated drinking water or food. In some cases, very large numbers of both adults and children in different parts of the world were affected. One common denominator in these incidents was skin changes characteristic of arsenic poisoning; however, a wide range of other symptoms which varied from area to area was noted. Vascular changes were reported, and in one area (Taiwan), peripheral vascular damage was described as the predominant clinical manifestation with extreme cases leading to blackfoot disease. Raynaud's phenomenon and acrocyanosis were also reported. In another area (Chile), an increased incidence of myocardial infarction among young adults was described. In some studies there were effects on the nervous system, mainly with manifestations of peripheral neuropathy, but also in one incident (Morinaga), manifestations of CNS effects were present several years after short-term high exposure. More studies are needed of CNS and liver damage. In Chile an increased risk of respiratory infections among children and also an increased occurrence of bronchiectasis were reported. A relationship to the reported immunosuppressive effect of arsenic among animals should be considered. Skin cancer was clearly connected to the arsenic exposure in Taiwan, but other complicating factors were also present. The above arsenic-related effects were reported to diminish when the exposure decreased or ceased, which supports an etiological relationship. In Lane County, Oregon, elevated drinking water concentrations of arsenic have been described to cause skin changes, and only rare cases of other possible clinical arsenic effects were reported. All these findings, together with data from cases with clinical arsenic treatment, indicate that arsenic has toxic potential to humans after environmental exposure via ingestion. It is known from chemical studies that arsenic exists in the environment in a large number of chemical forms and this may partly explain the reported differences in symptomatology. With few exceptions, no speciation studies of the arsenic compounds ingested by humans have been reported. The epidemiological methods were not always comparable between the studies, and hence a thorough correlative evaluation is difficult to make.

Other epidemiological data clearly indicated that exposure to airborne arsenic in the presence of other metals and irritating substances like sulfur dioxide was associated with an increased incidence of lung cancer among industrial workers. There was a strong indication of a causal link between these environmental factors and lung cancer. In one area surrounding a smelter (Toroku), epidemiological

studies have also shown tendencies for increased mortality in lung cancer among non-occupationally exposed persons. These data need further analysis and confirmation before definite conclusions can be drawn, because similar studies of human populations living around a smelter in Sweden have not shown this effect. Findings of hearing impairment among children were reported from an area (Czechoslovakia) with high ambient air concentrations of arsenic-containing fly ash released from a power plant burning coal with unusually high arsenic content. The hearing changes, however, were very minor and need confirmation. In the same area, slowed growth development of children was reported, and this was also found in another study (Toroku).

The toxic potential of arsenic after inhalation exposure was evident. In order to define the needs for preventive action, further studies concerning the effects of arsenic in different exposure situations and characterization of the arsenic species involved are urgently needed.

Differences in race, climate, nutrition, etc., in the different areas may account for the disparity in findings so far. Joint international efforts are needed to carry out long-term follow-up studies in areas with arsenic exposure via water and food as well as industry. A country with populations receiving high exposures may then benefit from analytical and other resources existing in other parts of the world. Further experimental and clinical studies into particular subclinical effects on the nervous system, liver, and skin as well as the mechanisms of arsenic-induced cancer are also greatly needed. Wherever possible, dose–response relationships should be quantified.

### Recommendations

The somewhat disparate clinical findings among human populations with chronic arsenic exposure stems in part from a lack of uniformity in the designs of the various studies. It is suggested that an international organization such as WHO take the initiative in standardizing such studies and disseminating accumulated information.

A second area of concern for such studies relates to the presence of other environmental factors which may modify human responses to arsenic and complicate interpretation of epidemiological data. The general environment of studied populations should be described as completely as possible with respect to complicating factors or agents.

Several factors should be considered when evaluating human exposure to arsenic based on arsenic content of biological indicator media (blood, hair, nails, urine). The exact relationships between route and dose-level of arsenic exposure and concentrations in various media are not well known and need further study. Hair analyses in populations exposed to airborne arsenic are complicated by absorption phenomena. Airborne arsenic also complicates measurements in other media due to the presence of respirable and nonrespirable fractions and the possible high gastrointestinal absorption of arsenic species in mucus cleared from the respiratory tract. Methods capable of integrating total absorption of arsenic from all possible routes should be developed. Work should be directed specifically towards assessing dose–response relationships.

Assessment of the carcinogenic potential of $As^{+5}$ as well as $As^{+3}$ should be conducted.

## Kinetics and Metabolism

### Summary

Data on turnover and metabolism of different inorganic and organic arsenicals in experimental animals as well as in man was reported. It was evident from these studies that the chemical speciation of arsenic changes after intake of inorganic arsenicals. Urinary excretion of arsenic in humans exposed to $As^{+3}$ or $As^{+5}$ was reported to be mainly in the form of methyl arsenic and dimethylarsinic acid. After ingestion of the organoarsenical found in crab meat, neither inorganic arsenic or methylarsenic or dimethylarsinic acids were excreted in urine but there was a marked excretion of total arsenic, thus indicating that the organoarsenical may be excreted without metabolic degradation.

Animal experiments with cacodylic acid (dimethylarsinic acid) showed that the major portion was excreted in urine within 24 hr.

The *in vivo* metabolism and toxicity of arsenic appears to be potentially mediated by a number of other elements. The interaction between arsenic and selenium is the most well studied. Under certain conditions concomitant administration of arsenic has been shown to diminish the toxicity of selenium, apparently by enhancing biliary excretion of the latter. Evidence of selenium diminishing the toxicity of arsenic is less clear, and indeed, dimethylselenium appears to potentiate arsenical toxicity. Synergistic interactions with cadmium also appear to occur. The effects of route of arsenical administration on the pharmacokinetics of arsenic were also discussed.

### Recommendations

Although the data at hand give a rough picture of arsenic metabolism in man and experimental ani-

mals, it is obvious that more work is needed to define the mechanism of these processes for different chemical species of arsenic.

Research is needed into the transfer of various arsenic species across the blood-brain and placental barriers since arsenic has been found to be teratogenic in animals.

Studies dealing with the mechanism behind the apparent adaptation to chronic low-level arsenic exposure are also needed.

Utilization of the rat for metabolic studies with arsenic should be performed with caution due to the peculiar high affinity of rat red blood cells for this element. Judicious use of this species for other types of studies is also recommended.

## Effects and Dose–Response Relationships in Animals

### Summary

A survey of domestic animal poisonings from arsenic in the United States disclosed that dogs and cattle were the species most commonly involved. The exposure of these animals to arsenicals appeared to result most frequently from accidental misuse or negligence in applying the compounds. Experimental studies in rats exposed intratracheally to flue dust, $As_2O_3$, or copper ore and the incidence of lung tumors, compared with controls or animals treated with benzo[a]pyrene were reported. Squamous cell metaplasia and lung adenomas were observed in the various treatment groups, but no firm conclusion concerning arsenic carcinogenicity in rats could be drawn. Several studies were presented dealing with the effects of chronic arsenic exposure on the structure-function of hepatic mitochondria. *In situ* mitochondrial damage was associated with decreased respiratory function for pyruvate mediated respiration which appeared to rise from arsenical inhibition of the pyruvate dehydrogenase complex. Perturbation of mitochondrial membranal marker enzymes was noted and related to the increased excretion of specific urinary porphyrins.

Teratogenicity of arsenic was discussed next. Injection of sublethal doses of $As^{+5}$ into hamsters, mice, and rats during gestation was found to produce embryo toxicity at higher doses and rather specific developmental anomalies at lower levels. The relevance of these findings to possible similar effects in humans exposed to arsenic was discussed and it was concluded that thorough studies of exposed populations were in order. Evaluation of offspring for behavioral changes and incidence of cancer in later life was recommended as well as correlations between placental and cord blood levels of arsenic and fetal malformations.

An excess of chromosomal aberrations and skin cancer was reported in persons exposed to As either therapeutically or occupationally many years earlier. Similar chromosomal aberrations were also reported in smelter workers. Reported effects of $As^{+3}$ on postreplication DNA repair in ultraviolet-irradiated *E. coli* suggested one possible mechanism for the chromosomal abnormalities. The need for further studies on mammalian DNA repair was noted.

### Recommendations

There is an urgent need for research concerning individual and species differences in biological responses (carcinogenicity, enzyme changes, physiological functions, etc.) to chronic arsenic exposure.

Further work is needed into the effects of arsenicals on developing organisms, and in particular the studies concerning cellular mechanisms of action.

Studies are needed in mammalian test systems which relate arsenical-induced cell death to its possible effects on DNA repair in rapidly dividing replacement populations.